

The economic impact of Irritable Bowel Syndrome

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Abbreviations

IBS: irritable bowel syndrome; HMO: Healthcare maintenance organisation; QoL: Quality of life

Key words:

Irritable bowel syndrome, health economics, healthcare utilisation, productivity, cost

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Abstract

Background: Irritable bowel syndrome (IBS) is a chronic functional disorder of the gastrointestinal system affecting a large number of people worldwide. Whilst it has no attributable mortality, it has substantial impact on patients' quality of life (QoL) and is associated with considerable healthcare resource use.

Aim: To review the economic impact of IBS, firstly on the individual, secondly on health care systems internationally and thirdly to society.

Methods: Appropriate databases were searched for relevant papers using the terms: Irritable Bowel Syndrome; IBS; irritable colon; functional bowel/colonic disease; economics; health care/service costs; health expenditure/resources; health care/service utilisation; productivity.

Results: IBS impacts most substantially on patients' work and social life. Reduction in QoL is such that on average patients would sacrifice between 10 and 15 years of their remaining life expectancy for an immediate cure. Between 15% and 43% of patients pay out-of-pocket for remedies. No studies quantify loss of earnings related to IBS. Direct care costs are substantial, 48% of patients incur some costs in any year with annual international estimates per patient of: USA \$742-\$7547, UK £90-£316, France €567-€862, Canada \$259, Germany €791, Norway NOK 2098 (€262) and Iran \$92. Minimising extensive diagnostic investigations could generate savings and has been shown as not detrimental to patients. Cost to industry internationally through absenteeism and presenteeism related to IBS is estimated between £400 and £900 per patient annually.

Conclusions: IBS is associated with substantial costs to patients, health care systems and society. Considerable benefit could be obtained from effective interventions.

Introduction

Irritable bowel syndrome (IBS) is a chronic functional disorder of the gastrointestinal system characterised by abdominal pain and altered bowel habit, with either predominantly diarrhoea, constipation or both. IBS has no attributable mortality¹ but it is important due to the effect it has on quality of life (QoL)^{2,3} and the large number of people it effects, with a global prevalence of 11%.⁴ With increased budgetary constraints on society and especially within health care systems it is important to consider the economic impact of such a prevalent condition.³

The economic impact of any condition is comprised of the costs that are attached to it. These costs fall into different domains so calculation will vary according to the perspective taken.⁵ Firstly there are costs incurred by the patient. These are the intangible cost to the individual in terms of reduced QoL,⁶ which includes reduced capacity to function in various roles, and direct financial cost through lost earnings and out-of-pocket expenses.⁷ Secondly, there is the direct cost of the health care, which can be considered in two ways. One is to account for the explicit cost to the healthcare provider calculated from unit costs of resources and time used. The other, more frequently used method, is to consider the price charged by the provider and incurred by a third party paying for healthcare provision, such as a government, insurer or health maintenance organisation (HMO). These costs are derived from published tariff or reimbursement prices or charges. These may be aggregate average prices for an average patient receiving that care and can include a mark-up to allow for profits, cost-sharing or to cover losses in other areas depending on the healthcare system.⁸ Costs from a third party payer perspective are those most easily available and most widely analysed.³ Finally there is the cost to society in terms of indirect cost from reduced productivity in the workplace, both from the individual with the condition but also due to time lost due to spill over effects on others in the patients' family. Indeed the cost to other family members may also include reduction in their QoL.⁵ Costs to society will also include those costs to sectors outside health, including education and social security.⁹

This review aims to assess the economic impact of IBS on the individual, healthcare system and to society and establishes common themes across different healthcare systems. For individuals, we describe how QoL is affected and quantify their out of pocket expenses and loss of earnings. We will outline the healthcare utilisation and direct costs to health care systems in different countries, specifically focussing on health care attendance, investigations and prescribed drugs. Finally, we will discuss absenteeism, presenteeism, industry and carer costs which all contribute to the wider costs to society of IBS. This synthesis of the available research evidence will outline the magnitude of the potential benefit that effective interventions in IBS could make.

Search strategy

This is a narrative review, but to ensure it reflects current literature a search was conducted in January 2014 of the following databases: NHS Economic Evaluation Database (NHS EED), Database of Abstracts and Reviews of Effects (DARE), International Agencies for Health Technology Assessment database (INAHTA), Cochrane Review, EMBASE and Medline. The search terms used were: (Irritable Bowel Syndrome OR IBS OR irritable colon OR functional bowel disease OR functional colonic diseases) AND (economic models OR economic* OR cost* OR health care costs OR health service costs OR health expenditure OR health resources OR health care utilisation OR health service utilisation OR productivity). These papers were limited to English language and abstracts were reviewed for relevance. References were checked to ensure all potentially relevant papers were retrieved. Grey literature sources were not searched.

Cost to the patient

Measuring quality of life and generating utility values

The emotional, social and physical dimensions of a person's life are captured through measurement of QoL. Changes in these domains due to an illness may be assessed either using a generic

instrument that can be generalised to all conditions or using an instrument specific to the illness of interest.¹⁰ To capture the impact of QoL reduction due to IBS in economic evaluation, these measurements need to be converted to utility values. The conversion of QoL measures into utilities describes quantitatively an individuals' preference for a particular health state under conditions of uncertainty,¹¹ an essential theoretical principle underpinning health economics.^{5,12} People are asked about their preferences for different health states and to trade time from their future life expectancy to avoid that state.¹³ Utility values are between 0 and 1, where 1 is equivalent to perfect health and 0 is death (negative scores do exist where patients feel a health state is worse than being dead) and these scores can then act as weights for quality in the calculation of quality adjusted life years.¹¹

The Euroqol-5 Dimensions (EQ5D) questionnaire has had all potential QoL outcome scores it may generate mapped to country specific utility values which allows comparison of utility across diseases and countries.¹³ Thus it supports economic analysis in a way that a disease specific instrument may not. EQ5D has been shown to be valid in IBS, it is sensitive to change in disease captured on disease specific instruments¹¹ and had good longitudinal validity.¹⁴ A change on the utility scale of 0.03 is the minimum for a clinically important difference in IBS.¹⁴

Quality of life and utility in IBS

IBS causes significant reductions in all dimensions of QoL.² In the USA, 68% of survey respondents reported missing 10 activities or social events on average over a 3 month period due to their IBS, equivalent to one activity per week.¹⁵ When questioned, the majority of IBS patients responding to a newspaper advert in the UK reported feeling angry about having IBS and fed up.¹⁶ Over two thirds of respondents reported at least some pain and half experienced at least moderate anxiety and depression.¹⁶ Due to the nature of their selection, these patients may not be representative of all people with IBS, but similar findings are seen across Europe and North

America.^{11,15,17} Compared to colleagues without IBS, the factor most significant in lowering QoL for workers with IBS in the US is reduction in their capacity to fulfil their physical roles.² The same was found in European patients with IBS from primary and secondary care, who also expressed lower perception of their own health than people without IBS.¹¹ The other factors substantially reducing their QoL were the impact IBS had on their work, social life and ability to travel.¹¹ Bowel symptom severity and psychological symptom severity have the most significant effect on reducing QoL in IBS patients, and if present together reduce QoL further in an additive manner.¹⁸

Studies across Europe and North America show reasonably consistent reduction in overall mean EQ5D scores compared to the general population of around 0.14-0.22.^{11,19} The overall mean values vary between 0.62 to 0.75.^{11,14,17,19} This compares to utility values of between 0.77 and 0.92 in patients with inflammatory bowel disease,^{20,21} 0.82 to 0.84 for patients with coeliac disease²² and 0.76 to 0.85 in patients diagnosed with potentially treatable colorectal cancer.²³ In IBS, a 0.2 point decrease in health utility on this score has been demonstrated between those with mild to moderate symptoms and those with severe symptoms.¹⁹ Mean baseline utility of between 0.62 and 0.75 is considered equivalent to a patient of 35 with an expected 40 years of life remaining being willing to sacrifice between ten years (if 0.75) and 15 years (if 0.62) for a permanent and immediate cure for their IBS.¹⁴ No significant difference in overall QoL or in the domains affected has been reported between patients younger than 50 years and those who are older.²⁴ IBS symptoms fluctuate over time, and it has been shown that without any intervention there is no real change in QoL in patients in the community or attending primary care over three months.^{14,25} Longer time intervals have not been assessed.

Out of pocket costs

Few studies have considered the direct out of pocket cost to patients with IBS. The majority of preparations used to control symptoms in IBS are available over-the-counter and many non-drug treatment options for IBS are available without the need to access health care systems (for example acupuncture), consequently community studies are most likely to reflect the true proportion of patients with IBS who take medication or access these services.⁸ Estimates suggest between 15%²⁶ and 43%¹⁷ of patients take over the counter remedies with almost two thirds of them buying laxatives, over a third analgesics and 32% buying more than three medications.¹⁷ The cost to the patient of acquiring these remedies has not been assessed. Along with medication costs, transportation to and from clinic appointments have not been considered. Similarly, some patients will choose to pay for alternative therapies or to see a physician or surgeon privately regarding their IBS and these costs, too, have not been measured.

Loss of earnings

Time off work, the need to reduce hours and changing roles due to IBS symptoms have all been reported,^{25,26} with as many as 12% of patients stopping work all together due to IBS.²⁶ Evaluation of these costs have been considered from the perspective of the employer, however and not through loss of earnings.

The intangible cost to the patient from reduced QoL is frequently measured and considered within economic evaluation. These indirect costs incurred by the patient, however, are not captured in third-party cost estimates and rarely fully assessed in societal evaluations.⁸

Cost to the provider or a third-party payer

Calculating direct costs

To calculate the direct healthcare costs of any condition, healthcare utilisation of patients with that condition must be measured. This can be done using community questionnaires, where patients

are asked directly about their patterns of healthcare use, from primary care or secondary care records or from administrative databases. Once the amount of healthcare utilization has been assessed, the cost of this care can then be calculated. As described in the introduction, direct health care costs can be calculated from the perspective of the provider or that of the payer. All of the studies of healthcare costs in IBS consider them from the point of view of the payer, either a national health service, HMO or third party payer. The difference between HMO costing and third party payer costing is that the HMO, like national health services uses tariff rates whilst third party payers use charges levied.

Differences in how healthcare systems are organised and financed are likely to cause some variation in the number of people choosing to consult with IBS symptoms and who they consult. Some healthcare providers, such as national health services and health maintenance organisations (HMO), may insist on consulting particular healthcare professionals with strict guidelines for further management once they present, whilst non-HMO insurance providers may allow greater freedom in whom a patient consults and the investigations and treatment they receive. Similarly as suggested above, some patients may choose to pay out of their own pocket to see a physician and the price differentiation may affect who they choose to consult and how much further healthcare they utilize. Despite these variations the trends in utilisation described above remain broadly similar.

Primary care

In the USA 25-49% of IBS patients consult a primary care physician in a year, with an average of 2-3 visits per year.²⁷⁻²⁹ This is a similar rate to that seen in people with asthma or migraine.⁷ Just under half of these consultations are directly related to IBS symptoms, with abdominal pain the predominant feature associated with consultation.²⁹ When questioned, over half of those patients not presenting for the first time said that they were re-attending because previous treatment was

unsatisfactory.²⁸ No significant variation in attendance has been demonstrated by IBS sub-type.²⁸ Overall, from a community based study in the USA, when compared to people without IBS, over the course of one year 17% more of the group with IBS will visit a physician.²⁹ On average in the UK patients with IBS will have slightly more than one additional attendance at primary care over a year than people without IBS.²⁵ There is scant data on consultation over longer periods, but one UK study shows that among those newly developing IBS over a ten year period, the median number of primary care consultations for IBS was only 1 with the maximum being 14.³⁰ These figures from the USA and the UK are somewhat lower than reported in Germany, where medical records showed that IBS patients had an average of 9 primary care visits per year.³¹ Primary care visits account for up to 30% of total direct healthcare costs for patients with IBS.^{6,31-33}

Secondary care

In the USA, during the year that patients are diagnosed with IBS, 19% will consult secondary care.²⁷ A study of primary care in the UK found that 30% of IBS patients were referred to secondary care where two thirds of them saw a physician and a third saw surgeons.³⁴ Patients who deny stress is associated with their symptoms,³⁴ men, those with diarrhoea, people taking medication and those seeking alternative therapy are all more likely to attend secondary care.¹⁶ Likelihood of being referred to secondary care falls by 6% every month after initial diagnosis.¹⁶ A survey of gastroenterologists in the North of England reported that these referrals accounted for 36% of all new patients and that on average each patient would have two visits.⁶

Emergency care

Few people require emergency care for IBS and it accounts for only a small number of hospital admissions. The proportion of patients with IBS receiving emergency care is broadly similar in Europe and North America, ranging from 2-5%.^{17,27,31} IBS patients who report moderate or severe abdominal pain are more likely to seek emergency care ($p < 0.05$).³⁵ Admission to hospital for IBS

occurs in 0.5-6.5%, with lower rates in North America than Europe^{6,17,27,31} Despite this low rate, the significant cost of inpatient care means it accounts for 25-30% of total healthcare cost for IBS.^{6,31}

Surgery

Rates for abdominal surgery are also higher in those with IBS than in those without, with IBS patients receiving twice as many appendectomies^{36,37} or hysterectomies³⁶ and 2-3^{36,38} times as many cholecystectomies. About a quarter of patients with IBS have gynaecological surgery and a third have an appendectomy or cholecystectomy.³⁹

Prescriptions

Whilst the cost of medication obtained over-the-counter is borne by the patient, prescription medications form healthcare costs to the provider, health service or the third party payer. Costs of medications received on prescription are more easily estimated than those obtained without because prescription data are recorded on the insurance claims or care providers' database, although these are not all collected by the patient. Between 33% and 91% of patients with IBS receive a prescription for medication in any year^{17,31,39} and on average, IBS patients will receive 3-7 prescriptions per year for medication to treat IBS symptoms.^{6,27,31} Compared to people without IBS this represents 2-3 more prescriptions over a year.²⁵ In the UK the most frequently prescribed medications are antispasmodics (30%) and laxatives (25%).⁶ Anti-diarrhoea agents are just 6% and antidepressants 3%.⁶

Investigations

In the USA during the year of diagnosis with IBS patients will have an average of six blood tests,²⁷ one outpatient procedure²⁷ and one radiological procedure specifically related to their IBS.

In Europe 63-84% of IBS patients receive a diagnostic procedure^{17,31,34} with half having abdominal ultrasound scans and over a third undergoing colonoscopy.¹⁷ Nearly 25% of colonoscopies in patients aged under 50 in the USA have previously been reported as being performed to investigate IBS,⁴⁰ despite evidence that colonoscopy in IBS has a low diagnostic yield⁴¹ and is unlikely to provide any reassurance to the patient.⁴² The USA may have different rates of colonoscopy to other countries due to a higher level of patient demand led investigations and incentives to provide investigations due to the reimbursement system.⁴³

The amount a patient is investigated for their IBS symptoms, and the subsequent cost, will depend on whether the physician is confident in making a positive clinical diagnosis.⁴⁴ In the USA 72% of physicians treat IBS as a diagnosis of exclusion⁴⁴ and these physicians were found to order between 1 and 2 additional tests on average compared to those confident in making a positive clinical diagnosis, costing an additional \$364 per patient.⁴⁴ A Danish study of primary care compared a diagnosis of exclusion shown to be frequently used in Western countries^{44,45} with a positive diagnosis following clinical guidelines.^{46,47} The total cost of the minimum number of investigations undertaken for a diagnosis of exclusion (coeliac, thyroid and liver screen, full blood count and inflammatory markers and lactase gene test, stool analysis and sigmoidoscopy) was \$913.59 compared to \$50.11 for clinical diagnosis supported by normal full blood count and inflammatory markers.⁴⁵ There was no significant difference in change in symptoms, severity or satisfaction between those receiving the minimal or more extensive investigations, either at one month or one year follow-up. During the following year neither group of patients had significantly different utilisation of healthcare resources, with the median total cost of care for those diagnosed by exclusion being \$127/patient compared to \$112/patient for those diagnosed positively ($p=0.70$).⁴⁵ After one year the additional investigations in those diagnosed by exclusion had identified organic disease in 10% of patients (10 lactose intolerance, 1 rectal adenoma and 1 parasitosis), none of the patients diagnosed using a positive clinical strategy had received further

investigation for ongoing or new symptoms.⁴⁵ These studies show that adhering to the current guidelines for diagnosing IBS from clinical findings with a normal full blood count and inflammatory markers in the absence of alarm features confers a significant cost saving without significant detriment to the patient.^{44,45}

Overall costs

Between a third and a half of people within the community who have symptoms that would be diagnostic of IBS will seek medical advice^{1,37,48,49} (range from 10%³⁷ to 70%⁵⁰) and those who do consult a physician tend to consult regularly. In any year, 48% of patients diagnosed with IBS will incur some direct medical cost from gastroenterological related healthcare⁵¹ and when non-gastrointestinal care is also considered, this increases to 88-94%.^{32,48}

Variations in estimates of overall direct healthcare cost are considerable (table 1). Studies from the USA estimate the annual cost per patient with IBS between \$742³² and \$7547,⁵² with a projected annual cost for the nation of \$1353million.⁵³ Estimates of annual costs per patient are more conservative elsewhere, with UK estimates between £90⁶ and £316,²⁵ France €567 to €862,⁵⁴ Canada \$259,³³ Germany €791³¹ and Iran \$92.⁵⁵ The mean cost for Norwegian IBS patients directly related to their IBS over 6 months is NOK 1049 (€131), but costs for comorbid conditions in the same patients is 14 times greater (NOK 14856 [€1857]).⁵⁶ National annual projections for the cost to a country of treating patients with IBS range from £45.6-£200million in the UK,^{6,25} €3.1-4.1billion in Germany³¹ and \$2.94billion in Iran. There is significant heterogeneity between these studies (table 1). The most important differences are between the year that the costs relate to, whether costs were those felt to be directly related to IBS care or all care, cost perspective, the population, the source of utilisation and cost data and whether mean or median costs were used as summary measures. This heterogeneity makes the reported estimates barely comparable but they do show that there is a substantial direct healthcare cost burden attributable to IBS. Health

care costs are higher in patients with IBS than those without IBS in all domains of health care utilisation.^{25,35} It is not surprising that patients with IBS have higher healthcare costs than people without IBS in the year that they are diagnosed, but this increased cost persists up to three years after diagnosis.^{27,57} Of the excess healthcare costs, 66-80% are not attributable to gastrointestinal complaints.²⁷ The increased utilisation of healthcare resources for non-gastrointestinal issues and the increased costs attached may reflect significant levels of comorbidity in patients with IBS,⁵⁶ including the burden of multiple functional conditions which tend to cluster in these individuals.⁵⁸⁻

60

The studies described here all calculate the cost per year for patients with IBS from whichever perspective is adopted rather than the cost of IBS per patient over a lifetime. Despite this, the evidence that direct costs for patients with IBS remain increased three years following diagnosis^{27,57} and are significantly higher than for people without IBS for non-gastrointestinal care as well as gastrointestinal care,^{6,25,27,32,35,61} would suggest that the cost of IBS over a patient's lifetime are considerable.

Societal costs

Taking a societal perspective to calculating the cost of an illness aims to capture the impact of that condition on the welfare of the whole of society, not just the individuals affected and the healthcare sector. The cost a condition places on society outside of the direct health care costs can fall in other sectors such as education, social services and industry. The effects on industry are commonly from loss of productivity of individuals within the workplace, either through absenteeism or through reduced functioning whilst at work, presenteeism. Productivity costs are especially important in conditions such as IBS that have a higher burden of morbidity than mortality.⁸

Absenteeism

Patients with IBS are twice as likely to take time off work as colleagues.²⁵ In Europe, between 15% and 50% of people with IBS require time off work due to their IBS symptoms.^{25,26,45,54} Far fewer, just 6% of Canadian patients report taking time off work due to IBS.¹⁷ One UK study found that whilst a greater proportion of people with IBS took time off work than those without IBS, on average the amount of time they took off was not statistically significantly different to those without IBS.²⁵ A larger study asking patients in a number of European countries, however, reported that patients with IBS took almost twice as many days off work over a year.³⁷ Around a quarter of patients take more than 3 days off due to their IBS symptoms annually,^{26,45} and 7% take more than two weeks.²⁶ In Europe and the USA patients with IBS take on average 3 to 4 extra days off work per year compared to colleagues without IBS.^{2,37} There is a statistically significant ($p<0.05$) association between the severity of IBS symptoms reported by a patient and the need to take time off work, with those experiencing severe symptoms requiring an average of one day off per month.⁶² Variation in employment law and sickness benefit provision may account for differences between rates in different countries and variation in sick pay provision or being self-employed may contribute to differences between individuals. Patients who respond to self-reported questionnaires, which make up the majority of these studies, are likely to be a biased sample, with one study reporting that over half of the respondents had daily symptoms,²⁶ suggesting they may be more likely to take time off work.

Presenteeism

Presenteeism is assessed by asking people how much of the time while at work they feel they were not performing to the best of their ability through either a reduction in the amount or kind of work they could do, accomplishing less than anticipated or being unable to work as carefully as usual due to symptoms of IBS during a specified period.^{19,63} This is a more subjective measure than absenteeism and estimates of time lost through presenteeism vary widely, with patients reporting between 2%⁵⁵ and 32%^{17,63} of their working week lost due to IBS symptoms. Severity of

IBS symptoms significantly increases presenteeism ($p < 0.001$)⁶³ and those with mild symptoms lose 7% less time than those with moderate or severe symptoms.¹⁹

Overall cost to industry

Assessing loss of productivity by combining measures of absenteeism and presenteeism due to IBS over a year and multiplying this by the average wage of the individuals provides an estimate of the annual cost to companies. One US national company calculated costs due to absenteeism in IBS patients in 1998 as \$901 per patient, 70% more than those without IBS.⁶⁴ Another in 2005 calculated their productivity loss attributable to IBS to be \$7737 per patient (95% CI &7332-8143).² By using the average population earnings the annual cost to society through productivity loss attributable to IBS can be generated. In Denmark the median annual cost is between \$1,360 and \$1,508 per patient from absenteeism.⁴⁵ Through absenteeism and presenteeism combined, the loss per IBS patient is estimated to be \$748 in Canada,³³ €995 in Germany³¹ and \$812 in Iran.⁵⁵

Carer burden

Most papers considering societal costs fail to consider the cost to those caring for or living with people who have IBS. One study has assessed 152 partners of patients with IBS, who had been together for an average duration of 20 years and compared their feelings of satisfaction and burden within the relationship to the partners of healthy controls.⁶⁵ Partners of patients with IBS reported feeling significantly more strained, distressed and under a greater burden than those of healthy controls. The level of burden expressed was reported to be comparable to partners of people with dementia and greater than the carers of terminal cancer patients.⁶⁵ This shows that there is likely to be an important impact on the QoL of partners.⁶⁵

Summary

IBS is a chronic condition that represents a significant burden to individuals, healthcare systems and society. QoL is substantially reduced for patients with IBS in all domains, which limits their daily activities. Patients with IBS utilise more healthcare resources than those without IBS for gastrointestinal symptoms and also for non-gastrointestinal related care which persists well beyond the first year following diagnosis. Patients with IBS are more likely to require time off work than people without IBS and report that when they are at work their symptoms considerably affect their productivity and ability to optimally perform their job. This loss of productivity is costly to the workplace and the employer and to society as a whole not only via the effects on the individual with IBS but also those caring for them. There is some evidence of the financial cost to patients in terms of out of pocket payments for over the counter medication, but this is limited and there is no data on cost to the patient of other therapies or costs related to transport and attending clinic appointments.

International guidelines emphasise positive clinical diagnosis for IBS and management within primary care. The findings that few patients investigated extensively for IBS symptoms have organic disease and that colonoscopies in these individuals almost always find no pathology would suggest that some of the extensive investigations and associated costs in patients with IBS are unnecessary and could indicate an area for cost reduction. There has also been some assessment of where costs fall within healthcare, with utilisation and costs being grouped usually into primary care, inpatient care, outpatient care, emergency care, prescriptions and procedures/radiology. Greater division of these costs, for instance by specialty and procedure type may provide targets for improved service provision or cost savings. Likewise, greater consideration of non-drug interventions is needed. Some such interventions have been shown to be effective in IBS management⁶⁶ and there is currently no evidence of how many people access them, who pays for this care and how much it costs. From a wider societal perspective, there are no studies that consider the impact IBS may have on education or other sectors outside of health, such as social

security. The benefit of filling these gaps in the literature would be to better inform future economic modelling for healthcare cost saving and resource allocation and to capture the full potential cost effectiveness of new interventions to the individual, the healthcare system and society.

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Author (publication year)	Country	Setting	Population	Perspective	Resources included	Currency (cost year)	Outcome
Talley (1995) ³²	USA	Community	536 responders to a postal questionnaire sent to randomly selected people from a computerised database of healthcare charges from one county (calculated to include 95% of county's population)	Third party payer	From computerised database of healthcare utilization and billing: primary and secondary care costs, out-patient costs assessed separately; laboratory and radiology costs.	US \$ (1992)	Overall median annual costs per patient = \$742 and \$893 excluding those with zero cost (\$429 and \$659 for those without IBS) Extrapolation to US white population annual cost \$8billion
Wells (1997) ⁶	UK	National Health Service	No one population of patients – aggregate utilisation and costs generated from general practice database and physician survey data	National Health Service	** only costs assumed to be directly related to IBS General practice survey: primary care consultations General practice database: prescriptions Gastroenterologist survey: out-patient attendance, inpatient care	UK £ (1995)	Mean total annual cost per patient = £90 Extrapolated annual costs for hospital sector = £20million Extrapolated annual UK population cost = £45.6million (0.1% total NHS annual expenditure)

Bentkover (1999) ³³	Canada	Primary and secondary care	120 medical records of IBS patients followed up for 5 years in primary care and 2 years in secondary care	Societal	<p>** only costs assumed to be directly related to IBS</p> <p>From medical records: All physician visits, Diagnostic tests, prescriptions, emergency visits</p> <p>Modelled calculations: costs of presenteeism and absenteeism</p>	Canadian \$ (1996)	<p>Modelled mean annual cost per patient:</p> <p>Direct medical costs = \$258.82</p> <p>Indirect (work place) = \$748.16</p> <p>Overall societal cost = \$1006.98</p>
Ricci (2000) ⁵²	USA	Administrative claims database	2770 patients from an administrative database of medical and pharmacy claims with first diagnostic record of IBS between 1 st July 1996-30 th September 1997	Third party payer	Claims database: physician visits, inpatient care, outpatient care, hospitalisation, medication,	US \$ (1997)	Mean annual cost per patient = \$7547
Levy (2001) ²⁷	USA	Health maintenance organisation	3153 incident IBS patients (enrolled patients with first diagnostic code for IBS in 1994 or 1995)	Managed care	From records of charges to insurer: Primary care visits, specialty visits, mental health visits, medications, laboratory tests, radiology, hospitalisation, emergency visits, GI and non-GI care	US \$ (1995)	Total mean annual health care costs per patient = \$3786 (\$1130 more than non-IBS controls)

Creed (2001) ⁶⁷	UK	Secondary care	257 patients with severe refractory IBS attending 7 GI out-patient clinics in Northern England enrolled for a trial of psychological therapy. Costs calculated for the year before trial entry	National Health Service	From primary and secondary care records: in-patient days, out-patient and day case attendance, A&E visits, GP visits, home visits, Nurse consultations, domiciliary care, day rehabilitation centre attendance, alternative therapy use, prescriptions Patient questionnaire: travel, non-prescribed medication, additional household expenditure including child and personal care, loss of wages and productivity loss.	Costs calculated in UK £ and converted to US \$	Mean direct annual health care costs: \$1743 Annual cost per patient due to lost productivity: \$334.50
Akehurst (2002) ²⁵	UK	Primary care	161 IBS patients diagnosed using ROME I criteria; 213 age sex and practice matched controls	National Health Service	From primary care records: primary care appointment; home visits; prescriptions; hospital outpatient by specialty; emergency attendances; inpatient episodes; time off work	UK £ (1997/98)	Mean annual cost per patient = £316.20 (£123/year more than controls) IBS patients average 1.5 days off work/month, not costed Scaled up annual population direct cost = £200million

Sandler (2002) ⁵³	USA	US population	National survey data for healthcare utilisation	Societal	National survey databases: inpatient care, outpatient visits, emergency care, procedures, prescriptions Indirect costs calculated from previously published ratio of direct to indirect costs in gastroenterology	US \$ (1998)	Annual total US population societal cost = \$1353million
Muller-Lissner (2002) ³¹	Germany	Primary and secondary care	200 randomly selected IBS patients with data extracted from medical records via structured interview with physician	Third party payer and Societal	From medical records (56% primary care; 44% secondary care): diagnostic procedures, outpatients by specialty, prescriptions, other therapy, hospitalisation, days off work as recorded in the medical records	€ (1999)	Total annual direct healthcare costs = €791.48 Total annual societal cost = €994.97 Scaled up total annual population cost (societal perspective) = € 3.1-4.1 billion
Patel (2002) ⁶¹	USA	Health Maintenance Organisation	501 patients with first IBS diagnostic code in 1998	Managed care*	From insurance claims data: emergency care, inpatient care, outpatient visits, prescriptions, procedures, laboratory tests)	US \$ (1998)	Annual median total cost per patient = \$2237-2504 (\$355-843 more than controls)
Leong (2003) ⁶⁴	USA	Administrative claims database	Employees and retirees of a national company and their spouses and dependents	Third party payer	Claims database reimbursements: physician visits, inpatient care, outpatient care, hospitalisation, medication, disability	US \$ (1998)	Annual overall total cost per patient = \$4527 (\$1251 more than controls)

			with diagnoses of IBS recorded		claims and cost of time lost from sporadic sick days and time at medical appointments		Annual cost of absenteeism \$901 (\$373 more than controls)
Longstreth (2003) ³⁵	USA	Health Maintenance Organisation	578 patients who has had a sigmoidoscopy in 2000 with ROME I defined IBS following postal survey (controls had sigmoidoscopy but not IBS on questionnaire)	Managed care*	From insurance claims database: outpatient visits by specialty, inpatient care, prescriptions, radiology, laboratory tests.	US \$ (2000)	Mean overall total annual costs per patient = \$3729.04 (adjusted: 51% higher than controls)
Le Pen (2004) ⁵⁴	France	French population	253 patients identified through a population survey	Third party payer and society	Questionnaires and patient interviews: physician visits, inpatient care, outpatient care, hospitalisation, medication, investigations, absenteeism	Euro (1999)	Average overall monthly direct medical costs per patient = €47.30 (95% CI 36.90-57.70)
Spiegel (2005) ⁵¹	USA	Secondary care	1410 consecutive IBS patients to gastrointestinal outpatient clinics	Third party payer	**only gastrointestinal costs considered Patient completed questionnaire: outpatient visit, procedures, radiology, surgery	US \$ (2004)	Mean total annual gastrointestinal costs per patient = \$3280.80
Roshandel (2007) ⁵⁵	Iran	Secondary care	Patients with ROME II defined IBS attending a	Societal	**only gastrointestinal costs considered	US \$ (2005)	Annual mean cost per patient:

			gastroenterology outpatient clinic (number with IBS not reported)		Patient interview: primary care visits, outpatient attendance, inpatient care, laboratory tests, radiology, prescriptions, days off work due to IBS, days working at 30% less than optimal function		<p>direct cost = \$92.04</p> <p>productivity loss = \$811.85</p> <p>overall societal cost = \$903.89</p> <p>Extrapolated population annual societal cost = \$2.94 billion</p>
Nyrop (2007) ⁶⁸	USA	Healthcare Maintenance Organisation	588 patients with ROME II defined IBS through patient questionnaire from stratified sampling of the health maintenance organisation database	Managed care* and assessment of out-of-pocket treatment costs	<p>Administrative claims: primary care visits, out-patient visit, in-patient care, emergency care, mental health service use, radiology, laboratory, prescriptions, other out-patient related costs. Gastrointestinal and non-gastrointestinal costs stratified</p> <p>Patient questionnaire: non-prescription medication, alternative treatments</p>	US \$ (2002)	<p>Mean total annual direct costs per patient = \$5049</p> <p>Mean annual out-of-pocket costs per patient = \$406</p>
Johansson (2010) ⁵⁶	Norway	Primary care	208 patients identified with IBS through questionnaires sent to primary care patients	National health service	Patient questionnaire and electronic medical records: investigations, consultations (primary and secondary care and alternative therapists),	NOK (2001 - in 2001 NOK 1 = €8)	<p>Mean overall 6 months IBS related costs = NOK 1049</p> <p>Mean overall 6 monthly total costs (IBS and non-IBS care) = NOK 15905</p>

					hospitalisation, prescribed and non- prescribed medication, days of sick leave		(median 6 monthly overall IBS related costs = NOK 0 [0-60468])
Begtrup (2013) ⁴⁵	Denmark	Primary care	302 patients aged 18-50 fulfilling ROME III criteria for IBS	National Health Service and societal analysis	Monthly patient questionnaires: GP consultations; specialist consultations; emergency visits; Investigations	US\$ (2012)	Median total direct costs over one year following diagnosis: Diagnosed by exclusion = \$127/patient Positive clinical diagnosis = \$112/patient Overall median total annual societal cost per patient diagnosed by exclusion = \$1614 positive diagnosis = \$1776

Table 1: Description and comparison of papers calculating the economic burden of IBS